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Tetrahedron Letters 48 (2007) 245–248

Tetrahedron Letters

Practical copper-catalyzed N-arylation of nitrogen heterocycles with aryl halides under ligand and additive free conditions

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Received 20 September 2006; revised 30 October 2006; accepted 9 November 2006

Abstract—N-arylation of a wide variety of nitrogen heterocycles with aryl iodides catalyzed by copper iodide under mild ligand and additive free conditions (^{n}Bu$_4$NBr, PhMe, NaOH, reflux, 22 h) was accomplished in good to excellent yields (up to 95%) and substrate conversions (up to 99%).

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The ability to construct N-arylated nitrogen heterocycles efficiently is currently an active area in organic synthesis due to the prevalence of this structural motif in a myriad of bioactive important natural products and pharmaceutically interesting compounds.[1] Among the various strategies developed to date, the copper-catalyzed Ullmann coupling reaction[2] has proven to be one of the most convenient synthetic routes for installing the *N*-aryl functionality.[2–9] However, such reactions have traditionally suffered from high reaction temperatures (typically above 140 °C), the need for stoichiometric amounts of copper catalyst that make scale up unfeasible and ecologically unfriendly, the use of toxic and air-sensitive aryl coupling reagents that can be difficult to access, and excess aryl halide starting materials to achieve reasonable product yields. In addition, low functional group tolerance and poor substrate generality that includes the lack of a general N-arylation method for each of the major classes of nitrogen heterocycles such as imidazoles, pyrazoles, and indoles, have lessened the utility of these methods.[2,3] In view of these shortcomings, the establishment of copper-mediated approaches under milder conditions has been actively pursued.[4–9] A recent notable achievement has been the use of 'Cu + ligand' (ligand = diamine or amino acid) catalytic systems by Buchwald[5] and Ma[6] who showed that the N-arylation of a variety of nitrogen heterocycles could be achieved in good yields. Following these pioneering works, a number of groups have reported similar approaches using a variety of diamines, Schiff-bases, [1,10]-phenanthroline, quinoline, aminoarenethiol, and oxime-phosphine oxide derivatives as ligands for Cu-catalyzed N-arylation of nitrogen heterocycles.[7] Despite these advances, examples on analogous reactions that do not require a ligand or additive in tandem with aryl halides as the starting materials have remained sparse. As a result of a long standing interest in metal catalyzed C–N bond formation in our group,[10] we report herein our preliminary findings on copper iodide catalyzed N-arylation of a variety of nitrogen heterocycles with equimolar amounts of aryl iodides in yields up to 95% that are comparable to those reported using ligand and additive promoted strategies.[5–7]

At the outset of this study, we found that treatment of pyrrole (1 equiv) with iodobenzene (1 equiv), 5 mol % CuI as catalyst, 5 mol % ^{n}Bu$_4$NBr as phase transfer catalyst, and NaOH (2 equiv) in toluene at reflux for 22 h gave the best result, furnishing *N*-phenylpyrrole in 95% yield (Table 1, entry 1).[11] Similar product yields were observed for reactions with catalyst loadings increasing to 10 or 20 mol % (entries 3 and 4) and at this latter catalyst loading with 3 equiv of NaOH (entry 6). Slightly lower product yields (68–73%) were obtained upon lowering either the catalyst loading of CuI to 1 mol % (entry 2) or NaOH to 1 equiv in the

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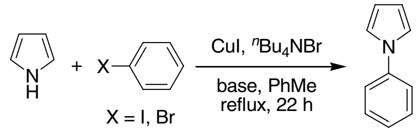
doi:10.1016/j.tetlet.2006.11.050

Table 1. Optimization of the reaction conditions[a]



Entry	CuI (mol %)	$^{n}Bu_4NBr$ (mol %)	Base[b]	Yield[c] (%)
1	5	5	NaOH (2)	95[d]
2	1	1	NaOH (2)	68
3	10	10	NaOH (2)	88
4	20	20	NaOH (2)	87
5	20	20	NaOH (1)	73
6	20	20	NaOH (3)	86[d]
7[e]	5	5	NaOH (2)	25[d]
8	5	—	NaOH (2)	4
9	20	20	K_3PO_4 (3)	49
10	20	20	K_3PO_4 (3)[f]	14
11	20	20	K_2CO_3 (3)	16
12	20	20	K_2CO_3 (3)[g]	—[h]
13	20	20	Al_2O_3 (3)	11
14	20	20	MgO (3)	6
15	20	20	$LiOH{\cdot}H_2O$ (3)	4
16	20	20	$MeCO_2Na$ (3)	—[h]
17	20	20	Pyridine (3)	—[h]

[a] All reactions were performed for 22 h with CuI:$^{n}Bu_4NBr$:base, molar ratio as stated in the table in PhMe at reflux.

[b] Values in parentheses denote the equiv of base used.

[c] ^{1}H NMR yield with CH_2Br_2 as the internal standard.

[d] Isolated yield.

[e] Reaction carried out with C_6H_5Br in place of C_6H_5I.

[f] Reaction carried out with K_3PO_4 in 5 mL of water.

[g] Reaction carried out with K_2CO_3 dried to a constant volume prior to use.

[h] No reaction.

presence of 20 mol % of CuI (entry 5). In contrast, when bromobenzene was employed as the aryl halide reagent, *N*-phenylpyrrole was afforded in a markedly lower yield of 25% (entry 7).

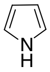
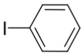
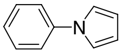
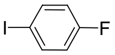
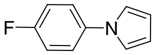
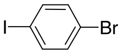
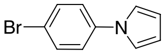
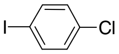
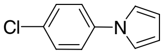
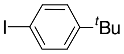
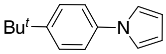
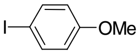
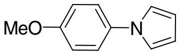
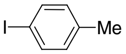
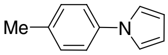
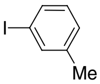
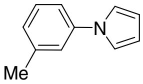
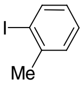
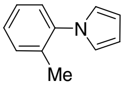
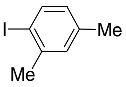
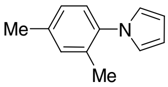
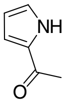
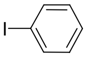
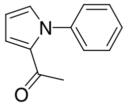
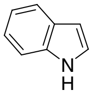
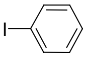
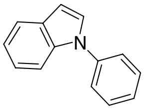
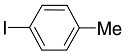
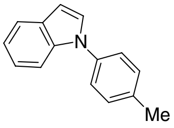
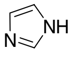
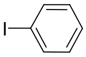
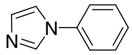
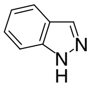
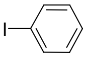
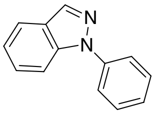
Inspection of entries 9–11 and 13–15 in Table 1 revealed that CuI-catalyzed coupling of pyrrole with iodobenzene and other inorganic bases was significantly less effective. Under the conditions of 1 equiv of pyrrole, 1 equiv of iodobenzene, CuI (20 mol %), and $^{n}Bu_4NBr$ (20 mol %) in toluene at reflux for 22 h, N-arylation with 3 equiv of K_3PO_4, K_2CO_3, Al_2O_3, MgO or $LiOH{\cdot}H_2O$ as a base gave *N*-phenylpyrrole in markedly lower yields of 4–49%. The reactions of pyrrole using either $MeCO_2Na$ or pyridine as the base are the only instances where no reaction was observed and both starting materials were recovered in quantitative yields (entries 16 and 17).

At this juncture, we would like to highlight that employment of $^{n}Bu_4NBr$ as a phase transfer catalyst and the presence of a small amount of water intrinsically present in commercially available inorganic bases was essential for the N-arylation reaction. Under our experimental conditions, when $^{n}Bu_4NBr$ was removed from the reaction and 1 equiv of pyrrole was treated with 1 equiv of iodobenzene in the presence of 5 mol % CuI and NaOH (2 equiv) in toluene at reflux for 22 h, *N*-phenylpyrrole was afforded in 4% yield (entry 8). Conducting the reaction under the same conditions as those for entry 11 in Table 1 but with K_2CO_3 dried to a constant weight under reduced pressure at 200 °C prior to use, on the other hand, gave no reaction (entry 12) while the use of 5 mL of a saturated solution of K_3PO_4 in water was also found to be detrimental and a low product yield of 14% was obtained (entry 10).

To define the scope of the CuI-catalyzed N-arylation reactions, we applied this process to a series of nitrogen heterocycles and aryl iodide derivatives (Table 2). These reactions afforded the corresponding N-arylated adducts in good to excellent yields (up to 90%) and substrate conversion (up to 99%) (entries 2–15). Notably, we were able to exploit the difference in reactivity of aryl halides ($I > Br \gg Cl > F$) in the present method by coupling pyrrole and the aryl iodide selectively in the presence of substrates containing aryl bromides, chlorides, and fluorides (entries 2–4). The electronic nature of the aryl iodide was also found to have no effect on the reaction yield (cf. entries 2–4 and 5–8). Furthermore, in instances where it was initially envisaged that the presence of a sterically demanding methyl group *ortho* to the iodine atom on the benzene ring of the aryl iodide would prevent coupling, the corresponding adduct was furnished, albeit in slightly lower yields (entries 9–10). Similarly, the N-arylation of sterically hindered 2-acetylpyrrole was shown to proceed smoothly to furnish the corresponding *N*-phenyl-2-acetylpyrrole in 50% yield and 70% substrate conversion (entry 11).

The application of our catalytic system for the N-arylation of other classes of nitrogen heterocycles was also examined (Table 2, entries 12–15). The reaction of

Table 2. CuI-catalyzed N-arylation of 1*H*-azoles with aryl iodides[a]

Entry	Azole	Aryl iodide	Product	Yield[b,c] (%)
1				95 (>99)
2				77 (>99)
3				90 (>99)
4				80 (>99)
5				86 (>99)
6				84 (>99)
7				88 (>99)
8				83 (94)
9				62 (87)
10				63 (88)
11				50 (74)
12				80 (>99)
13				64 (73)
14				84 (88)
15[d]				50 (80)

[a] All reactions were performed for 22 h with CuI:$^{n}Bu_4NBr$:azole:aryl iodide:base, molar ratio = 1:1:20:20:40 in PhMe at reflux.

[b] Isolated yield.

[c] Values in parentheses denote substrate conversion based on the amount of aryl iodide consumed as determined by ^{1}H NMR analysis.

[d] Reaction carried out with DMSO in place of PhMe as the solvent.

1 equiv of indole with 1 equiv of either iodobenzene or *p*-iodotoluene and 5 mol % CuI, 5 mol % $^{n}Bu_4NBr$ and NaOH (2 equiv) in toluene at reflux for 22 h, was shown to proceed to give the corresponding N-arylated products in 80% and 64% yield with near quantitative and 73% substrate conversions, respectively (entries 12 and 13). Under similar conditions, the coupling reactions of imidazole and indazole were found to give

N-phenylimidazole and *N*-phenylindazole, respectively, in good yields and substrate conversions; in the latter example, DMSO was used as the reaction medium due to the poor solubility of indazole in toluene (entries 14–15).

In summary, we have demonstrated a practical and straightforward CuI-catalyzed method for the N-arylation of nitrogen heterocycles with aryl iodides that proceeded in good to excellent product yields. The present protocol is applicable to a variety of nitrogen heterocycles and aryl iodides containing electron donating and electron withdrawing, and sterically demanding substrate combinations under mild conditions. A detailed examination of the scope of the present reaction is currently underway and will be reported in due course as part of a full letter.

Acknowledgements

This work is supported by a College of Science Start-up Grant and a University Research Grant (RG55/06) from Nanyang Technological University. The authors would like to thank Ms. Sheena Chee and Ms. Shiya Mak (Ngee Ann Polytechnic, Singapore), for their help in purifying some of the compounds reported in this work.

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11. *Typical experimental procedure*: To a round bottomed flask containing the nitrogen heterocycle (15 mmol), aryl iodide (15 mmol), CuI (0.75 mmol), $^{n}Bu_4NBr$ (0.75 mmol) and NaOH (30 mmol) under a N_2 atmosphere was added toluene (10 mL). The reaction mixture was vigorously refluxed for 22 h. On cooling to room temperature, saturated NH_4Cl solution (50 mL) was added and the organic layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by flash column chromatography to afford the N-arylated product.